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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,613	FARID ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-43,45-50,52-56,65-70,72-74 and 76-80* is/are pending in the application.

4a) Of the above claim(s) *11-24,27-43,46-50,52-56,65-70,72-74 and 76-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-10, 25, 26, 45, and 81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-43, 45-50, 52-56, 65-70, 72-74 and 76-80 are pending.
Claims 11-24, 27-43, 46-50, 52-56, 65-70, 72-74, and 76-80 are withdrawn.
Claims 1, 4-10, 25, 26, 45, and 81 are examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 12/14/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. This Office Action presents new grounds of rejection (from those rejections set forth in the Advisory Action of 11/06/2007). Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Declaration of Alan John Mileham filed under 37 CFR 1.132

1. The Declaration of Alan John Mileham, filed on Sep. 26, 2007 under 37 CFR 1.132 has been considered. The evidence provided in the declaration is addressed in the Response to Remarks later in this Office Action.

Maintained Claim Rejections - 35 USC § 112 1st Enablement

2. Claims 1, 4-10, 25, 26, 45, and 81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for methods of analyzing the reproductive longevity of a pig comprising assaying for the presence of a thymidine in the IGF-1R gene at position 3832 of SEQ ID NO: 23.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for determining the reproductive longevity of pigs comprising analyzing polymorphisms in the IGF-1R gene at position 3832 of SEQ ID NO: 23.

The claims encompass detection of homozygous and heterozygous genotypes at position 3832 of SEQ ID NO: 23.

The nature of the claims requires the knowledge of an association between nucleotide content at position 3832 of SEQ ID NO: 23 of a pig IGF-1R gene sequence and the reproductive longevity of the animal.

Direction provided by the specification and working example

The specification teaches an analysis (p. 52 – Example 2) of the IGF-1R gene sequence in ten pigs: Five living sows with high parity numbers and five animals culled for reproductive reasons representing high reproductive longevity and low reproductive longevity, respectively. And while the specification teaches that 'reproductive longevity'

means a biologically significant increase in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species (p.16), the reference does not teach any particular numbers for the parity of the sows used in the example. The reference teaches the identification of five polymorphisms in the pig IGF-1R gene in the ten sows examined, and further teaches that each polymorphism was assayed over a larger sample of animals from the same population to look for evidence of an association with increased reproductive longevity. The specification does not provide any details about this subsequent examination, or any results pertaining to the study.

The specification further teaches an analysis of a polymorphism (indicated as 'SNP 3832'; a C to T change at position 4889 of SEQ ID NO: 7; Figure 7C) in pigs (Example 3, p.55-56). The specification asserts that 'Allele 2' of the gene (T at position 4889 of SEQ ID NO: 7; presence of a FokI site in a fragment amplified with SEQ ID NO: 21 and 22) is positively associated with longevity. However, the specification indicates that in an analysis of 996 sows from four different farms, the determine effect is overestimated due to the data structure (p.55, lines 10-11). Example 3 further teaches the association of 'Allele 2' in boars and increased numbers of parities from the sows sired by the boars 'Allele 2'. The specification asserts that there is a positive association between sow homozygosity and reproductive longevity ($p=0.062$), but the specification does not teach that the genotypes of any of the sows in this second study of SNP 3382 was in fact determined.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of any particular nucleic acid sequence, or the detection of a polymorphism in a particular sequence is high, the level of unpredictability with regard to associating the presence of a nucleic acid sequence or any particular polymorphism with a phenotype, such as a measure of reproductive longevity, is even higher.

The prior art does not teach any reliable association between the IGF-1R gene, or polymorphisms thereof, and reproductive longevity in pigs.

The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Even in cases where an association between a particular gene and a phenotypic state is known to exist, such as with the LPL gene and heart disease risk or the β-globin

gene and sickle cell anemia, researchers have found that when using polymorphism analysis it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi (1998)). Furthermore, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be phenotype-associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p-value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for mutations within the same gene, it is highly unpredictable as to whether a particular mutation will be associated with a phenotype.

And while the specification asserts an association between the T allele of SNP 3832 and reproductive longevity in the two studies of Example 3, it is relevant to point out that the analysis of the pig IGF-1R sequence presented in Example 2 does not teach the identification of this position as polymorphic in the pigs examined in Example 2. Additionally, the data presented for the second analysis (using over 19,000 sows from 179 sires) indicates an association with a p-value of P=0.062. Thus, while the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference

point of 0.05 would not be considered strong enough for the basis of a conclusion) the instant specification does not teach consistent and significant correlation of SNP 3832 with reproductive longevity in pigs.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. Within the scope of the claimed invention, one would have to establish that the particular nucleotide content of a thymidine at position 3832 of SEQ ID NO: 23 is in fact indicative of reproductive longevity potential in any particular population of pigs. One would have to perform case:control studies with a large number of animals to determine a statistically significant association between the required nucleotide content and reproductive longevity (as determined by a significant increase in the number of pregnancies and/or the duration of time an animal is capable of reproduction, relative to the mean of a given population, group or species) as well as an association with any traits associated with reproductive longevity. The specification does not clearly teach a consistent and significant association of the required nucleotide content with reproductive longevity, and thus such experimentation would be required of any pig population of interest, where there is no assurance that any association will be found in different populations.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the

specific working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks and Declaration

3. Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments and the Declaration submitted in support of the arguments have been considered but are not found to be persuasive.

Applicants' initially argue (p.15 of Remarks) the claims require are drawn to a method requiring the particular nucleotide content of a thymidine at position 3832 of SEQ ID NO: 23. It is noted that the portions of the rejection regarding methods that encompass other nucleotide content have been withdrawn from the rejection as presented in this Office Action. Applicants further argue that the specification is fully enabling for the claimed methods, and have provided the Declaration of Alan John Mileham in support of that argument.

4. The Declaration under 37 CFR 1.132 filed 09/26/2007 is insufficient to overcome the rejection of claims 1, 4-10, 25, 26, 45, and 81 based upon 35 USC 112 1st ¶, as set forth in this Office action.

Initially it is noted that the Declaration (parts 5 and 6 on pages 2-3) provides that the data in the first analysis of Example 3 is in fact statistically significant, in support of the arguments of p.15 of the remarks that while the effect of the allele is overestimated, the p-value of the association in this population is accurate and significant. This argument, in light of the Declaration, is persuasive, and this portion of the rejection,

regarding the first analysis of Example 3, is withdrawn from the rejection as set forth in this Office Action.

Applicants' arguments further address the data presented in the second analysis of Example 3. However, the arguments (p.16-17 of Remarks) and evidence of the Declaration (part 7 on page 3) do not support the conclusion that there is a statistically significant association between thymidine at position 3832 of SEQ ID NO: 23 and reproductive longevity or days to culling. As noted in the rejection, the accepted p-value for indication of significance is $p \leq 0.5$. In the case of the example of the specification, the p value is p=0.062, which does not meet the accepted value as being statistically significant. Neither of the two additional analyses presented in the Declaration meet the accepted value as being statistically significant, with p-values of p=0.053 and p=0.550 or p=0.832 (additive or dominant). These results demonstrate the unpredictability of using the required nucleotide content to determine reproductive longevity in pigs, where the Declaration and arguments summarize this unpredictability, stating (in the Declaration):

> The lack of consistency between L02 and L03 in this study is not an uncommon occurrence. The fact that different single nucleotide polymorphisms (SNPs) (within the same gene or in different genes) have different effects in different breeds, lines or crosses tends to be the rule rather than the exception, and does not negate the value of this marker when used with appropriate sampling

In the instant case, it is this required 'appropriate sampling', where it is entirely unpredictable as to what breed, line, or cross, of any particular pig population will display any significant association, provides for the unpredictability of the claimed method. The claims are generically drawn to the analysis of pigs, and have to requirement of any particular breed, line, or cross. There is no nexus between the

breadth of the claim (generically encompassing any pig) and this unpredictability as to whether or not an association will be present in the pig. Thus, because of the unpredictability, the artisan using the claimed methods would have to perform the undue experimentation of actually establishing, in any pig population, the nature of the relationship between the thymidine at position 3832 of SEQ ID NO: 23 and reproductive longevity, where there is no assurance that any relationship would be found in any different pig breed, line, or cross.

As such, in light of the examples of the specification, and the further evidence provided in the Declaration, the rejection as set forth ins **MAINTAINED**.

New Claim Rejections - 35 USC § 102

In the rejection of claims under 35 USC 102, as noted in the MPEP 211.02, 'a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone'. Further, in Pitney Bowes Inc. v. Hewlett-Packard Co., 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, 'then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation'.

Additionally, the required steps of the claimed methods are noted. While independent claims 1, 24, and 45 recite a clause of identifying (claim 1) or inferring (claims 25 and 45) properties of a pigs 'if' the pig possesses certain nucleotides content, these claims require only assaying for the presence of the polymorphism (claims 1 and 25) or detecting the presence or absence of the polymorphism (claim 45). The claims thus do not in fact require that a thymidine is detected, and the correlation between the thymidine and the pig property is conditional upon the detection of the thymidine. Independent claim 81 requires only the step of assaying for the presence of a genotype, and does not require actually detecting any particular genotype. Applicants may wish to amend the claims such that they require steps of detecting the required nucleotide content, and correlating the detected content with the required reproductive longevity property.

5. Claims 1, 4, 25, 26, 45, and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Harumi et al (2001 as cited in the IDS).

Harumi et al teaches an analysis of the pig IGF-1R gene sequence using RT-PCR analysis of the cDNA sequence, and the identification of polymorphic positions within the sequence. The reference teaches analysis of a C/T polymorphism at position 3832.

Regarding claims 1, 25, 45, and 81 the reference teaches a method comprising obtaining a sample of genetic material from an animal (p.386, right column, first paragraph), and analyzing the nucleotide content at position 3832 by sequencing an RT-PCR product, where the sequence analysis is assaying for the presence of the polymorphism (claims 1 and 25), detecting the presence or absence of the polymorphism (claim 45), and assaying for the presence of a genotype (claim 81) (p.388, left col.; Fig 2).

Regarding claim 4, the reference teaches assaying by direct sequence analysis (p.388, left col.).

Regarding claim 26, the reference teaches assaying comprising gene amplification with a forward and reverse primer (Fig 1; p.388, left col.).

Claim Rejections - 35 USC § 103

It is noted that this Office Action rejects claims under 35 USC 112 1st ¶ for lack of enablement. While the claims are properly rejected for lack of enablement based on the association between nucleotide content and phenotype (i.e. thymidine at position 3832 of SEQ ID NO: 23, as asserted in the specification and encompassed by the

claims), the claims are also properly rejected under 35 USC 103 in so far as they encompass the detection of other nucleotide content which is not required for the phenotype association.

6. Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harumi et al (2001 as cited in the IDS) in view of Mackie et al (1999).

Harumi et al teaches an analysis of the pig IGF-1R gene sequence using RT-PCR analysis of the cDNA sequence, and the identification of polymorphic positions within the sequence. The reference teaches analysis of a C/T polymorphism at position 3832. Harumi all of the limitations of claims 1, and 4, from which rejected claims 5-10 depend. Harumi et al further teaches the sequence of the pig IGF-1R gene AB003362 (Fig 1).

Regarding claims 9 and 10, Harumi teaches the amplification of a gene portion containing the polymorphism using forward and reverse primers (Fig 1).

Harumi et al does not teach methods including RFLP and SSCP.

However, such methods for polymorphism analysis were well known in the art at the time the invention was made.

Mackie et al teaches methods for the analysis of polymorphic nucleic acid sequences.

Regarding claims 5 and 6, Mackie et al teaches RFLP (claim 5) and SSCP (claim 6) in the analysis of nucleic acid polymorphisms (p.12).

Regarding claims 7 and 8, Mackie et al teaches the steps of RFLP analysis including digestion of nucleic acid with a restriction endonuclease, and separation of the digested fragments to detect a pattern, and comparison of digestion patterns (Fig 5,

p.12 – PCR-RFLP). Regarding claim 8, the reference specifically teaches gel electrophoresis.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the known pig IGF-1r polymorphism at position 3832, as taught by Harumi et al, using the RFLP and SSCP methods of Mackie et al. One would have been motivated to use the methods of Mackie et al based on the assertion of Mackie et al that such methods are rapid, easy to use, and not expensive (p.14 – Future perspectives). Regarding the limitation in claim 7 that a restriction pattern of a sample is compared to a pattern associated with reproductive longevity potential, it would have been obvious to compare the patterns of CC, CT, and TT genotypes of the pig IGF-1R gene, where the genotype are taught by Harumi et al. If, as asserted in the specification, one of the genotypes is associated with reproductive longevity potential, then such an association is an inherent property of the genotype.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Examiner, Art Unit 1634

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